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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,998	05/02/2006	Vincent Cool	05-1083	3592

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EXAMINER	
NIEBAUER, RONALD T	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,998	COOL ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8,12-16 and 19* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-8,12-14,16,19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments and arguments filed 6/16/10 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn. Applicants amendments are sufficient to overcome the previous 102 and 112 2nd rejections. Previously, (9/30/08) applicants elected a benzyltrimethylammonium salt and Fmoc protecting group. In the instant case, each of the elected species was found in the prior art or found to be obvious based on the prior art. Any art that was uncovered in the course of searching for the elected species that reads on non-elected species is also cited herein. In accord with section 803.02 of the MPEP, the Markush-type claims have been examined with respect to the elected species and to the extent necessary to determine patentability.

Since applicant elected Fmoc, claims 14-15 do not read on the elected species. Since the art reads suggests the species recited in claim 14 it is included in this rejection.

Claim 15 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/30/08.

Claims 1-2,9-11,17-18 have been cancelled.

Claims 3-8,12-14,16,19 are under consideration.

Claim Rejections - 35 USC § 103

Claims were previously rejected under 103 based on the references cited below. The rejection is updated based on the claim amendments.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-8,12-14,16,19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rink (US 5,004,781) and Mihala et al (Journal of Peptide Science 'An alternative solid phase peptide fragment condensation protocol with improved efficiency' 7:565-568 (2001), cited in previous office action) and Merrifield et al (J Org Chem 'The limits of reaction of radioactive dicyclohexylcarbodiimide with amino groups during solid-phase peptide synthesis' v42 (1977) pages 1291-1295) and Finger (US 4,218,400).

Rink teach that the Merrifield synthesis of peptidic compounds is known (column 1 lines 43-column 2). Rink teach that the process includes the removal of an N-terminal protecting group (column 1 lines 51-52), another amino acid is added until the desired sequence is obtained (column 1 lines 62-64), and the peptide is removed from the support (column 1 lines 53-54). In the examples, Rink teach that there are wash steps after the cleavage and coupling steps (column 14 lines 24-41). Rink recognizes the use of Fmoc as a protecting group (column 8 line 42 , example 6). Rink teach (column 5 lines 7-25, column 8 lines 24-51) that benzyltrimethylammonium hydroxide, for example, can be used to remove the amino protecting group, for example Fmoc. Rink expressly teach that the use of benzyltrimethylammonium hydroxide for cleavage can be carried out at lower temperatures and can be concluded after a much shorter reaction time (column 5 lines 22-25).

Although Rink refer to the use of benzyltrimethylammonium hydroxide, Rink does not expressly use benzyltrimethylammonium hydroxide in a specific example. Rink does not teach the use of benzyltrimethylammonium hydroxide at any and all steps of the process.

Although Rink does not expressly reduce to practice with benzyltrimethylammonium hydroxide, Rink suggests the use of benzyltrimethylammonium hydroxide (column 5 lines 7-25, column 8 lines 24-51) for removing the N-terminal protecting group. In fact, Rink teach advantages of using benzyltrimethylammonium hydroxide (column 5 lines 7-25, column 8 lines 24-51). Thus one would be motivated to use benzyltrimethylammonium hydroxide to remove the amino protecting group during peptide synthesis. Rink recognizes some of the challenges of solid phase peptide synthesis including the difficulties in synthesizing longer peptides (column 2 lines

28-30) and problems with selectively detaching the peptide from the support (column 2 lines 23-27). Thus one would be motivated to address these known problems.

Mihala also teach solid phase peptide synthesis (title). Like Rink, Mihala recognizes that the problems with synthesizing long peptides includes decreasing solubility and associations (via van der Waals and hydrogen bonding) between the peptide chains (page 565 first paragraph). Mihala teach that the success of solid phase synthesis is limited by the aggregation of the growing peptide chains (abstract, page 565). Mihala teach that protected amino acids (page 566 section 'general') were used and that coupling steps were carried out with tetrabutyl ammonium salt additive (TBA*ODhbt) (page 566 section 'solid phase synthesis'). Mihala teach that the tetrabutyl ammonium salt additive is used to enhance solubility (page 567 first complete paragraph). Mihala teach that the tetrabutyl ammonium salt additive lead to improved efficiency (title, abstract, Table 1). Mihala suggests that use of the ammonium salt as an additive provides an alternative for improving coupling efficiency in solid phase peptide synthesis (last paragraph page 567). Further, it is noted that the art recognizes the use of salts in many column purification and other separation strategies for improved separation.

Taken together, both Rink and Mihala teach peptide synthesis and the use of ammonium salts during the process. Rink teaches an ammonium salt for the cleavage steps and Mihala teach an ammonium salt to enhance solubility and prevent aggregation. Since aggregation can be a problem at all steps of the process one would be motivated to enhance solubility throughout the process.

Merrifield also teach solid-phase peptide synthesis (title). Merrifield teach (abstract) the use of an ammonium salt (quaternary ammonium hydroxide) during peptide synthesis.

Importantly Merrifield teach that the presence of the triton B enabled a particular reaction to occur (abstract). Merrifield teach (page 1293 section 'acylation') that a resin bound peptide prepared by solid phase synthesis was reacted with Boc-Ala in the presence of Triton B. Merrifield teach (page 1293 section 'acylation') that the Triton B enables the chemical reaction. Merrifield teach (page 1294 section 'acylation of amidino peptide resins') that the product was cleaved from the resin and identified using chromatography. Merrified teach that Triton B is a quaternary ammonium hydroxide, but does not disclose the exact structure of Triton B. Finger (US 4,218,400) teach (column 2 lines 9-11) that Triton B is benzyl-trimethyl-ammonium hydroxide. Thus Merrifield teach the use of an ammonium salt during the addition step of the synthesis.

Taken together, Rink and Mihala and Merrifield teach peptide synthesis and the use of ammonium salts during the process. Rink teaches an ammonium salt for the cleavage of the amino protecting group and advantages of using benzyltrimethylammonium hydroxide (column 5 lines 7-25, column 8 lines 24-51); Mihala teach an ammonium salt to enhance solubility and prevent aggregation. Since aggregation can be a problem at all steps of the process one would be motivated to enhance solubility throughout the process. Merrifield teach that an ammonium salt enables the chemical reaction for the synthesis.

Rink teach the basic steps of solid phase synthesis. Rink teach that the process includes the removal of an N-terminal protecting group (column 1 lines 51-52), another amino acid is added until the desired sequence is obtained (column 1 lines 62-64), and the peptide is removed from the support (column 1 lines 53-54). In the examples, Rink teach that there are wash steps after the cleavage and coupling steps (column 14 lines 24-41). Thus Rink teach steps a-d of

claims 3-8. Since Rink teach that another amino acid is added until the desired sequence is obtained (column 1 lines 62-64), and the peptide is removed from the support (column 1 lines 53-54) Rink teach the steps as in claim 16. Rink teach (column 14 line 24) that washing is performed to remove the Fmoc group. Thus, one would recognize that a wash step is not necessarily required for the step as recited in claim 19. It is noted that step 16b includes a wash step as recited in claim 3. Rink recognizes the use of Fmoc as a protecting group (column 8 line 42 , example 6) as in claim 13 and Boc (example 6) as recited in claim 14. Rink motivate the use of benzyltrimethylammonium hydroxide (column 5 lines 7-25, column 8 lines 24-51) during the cleavage step since it allows for a lower reaction temperature and shorter reaction time. Thus, Rink teach a salt as recited in the instant claims. One would be motivated to include benzyltrimethylammonium hydroxide in the cleavage step (step a of the instant invention) as recited in claims 3,5. One would have a reasonable expectation of success since Rink expressly suggest the use of benzyltrimethylammonium hydroxide in the cleavage step and state that it allows for a lower reaction temperature and shorter reaction time. Since Rink recognizes that one of the challenges of solid phase peptide synthesis including the difficulties in synthesizing longer peptides (column 2 lines 28-30) one would be motivated to use the teachings of Mihala who teach that an ammonium salt additive is used to enhance solubility (page 567 first complete paragraph). Since Rink already teach the use of an ammonium salt one would be motivated to use the specific salt as taught by Rink. One would have a reasonable expectation of success based on the teachings of the references. Since solubility and aggregation are potential problems at various stages one would be particularly motivated to include the salts during the washing steps as recited in claims 6,8,12. Further, since Merrifield teach (page 1293 section 'acylation')

that Triton B (i.e. benzyltrimethylammonium hydroxide) enables the chemical reaction one would be motivated to use the benzyltrimethylammonium hydroxide during the addition steps as recited in claim 7. One would have a reasonable expectation of success based on the express teachings of Merrifield.

In summary, Rink Mihala and Merrifield all teach the well-known solid phase peptide synthesis technique. The references teach advantages of including salts specifically ammonium salts at various stages of the process. Rink teach (column 5 lines 7-25, column 8 lines 24-51) that benzyltrimethylammonium hydroxide can be used to remove the amino protecting group. Rink expressly teach that when benzyltrimethylammonium hydroxide is used that the cleavage can be carried out at lower temperatures and can be concluded after a much shorter reaction time. Merrifield also teach the use of benzyltrimethylammonium hydroxide, specifically during the addition step to enable the chemical reaction (page 1293 section 'acylation'). Further, Mihala addresses the problem of aggregation by using an ammonium salt to increase solubility and decrease aggregation. Since the references show that the art recognizes the use of ammonium salts as additives at various stages of the peptide synthesis process one would have a reasonable expectation of success.

It is noted that the claims state that the washing is 'thorough'. 'Thorough' is defined (page 2 of specification) as effective to remove reagents from the previous step. Since Rink teach effective synthesis of peptides and analysis of products the washings are necessarily thorough to allow for effective synthesis.

Response to Arguments 103 rejection

Applicants (pages 10-12) recite portions of the Rink reference and argue that Rink does not pertain to the subject matter of the instant claims.

Applicants argue that Mihala teach an example that uses a chloroform-phenol solvent system and a different salt and thus teaches away.

Applicants argue that the effect of the salt in the instant invention is different than in Mihala since the salts of the instant invention improve the elimination of excess of amino acids or cleavage reagents.

Applicants argue that the references do not teach the use of ammonium salts during the process and Merrifield does not make up for the deficiencies.

Applicant's arguments filed 6/16/10 have been fully considered but they are not persuasive.

Although Applicants (pages 10-12) recite portions of the Rink reference and argue that Rink does not pertain to the subject matter of the instant claims, it is first noted that the title of Rink recites 'Use in Solid Phase Peptide Synthesis'. Further, Rink expressly teach solid phase synthesis steps (column 14 lines 24-41). Importantly, Rink teach (column 5 lines 7-25, column 8 lines 24-51) that benzyltrimethylammonium hydroxide, for example, can be used to remove the amino protecting group, for example Fmoc. Rink expressly teach that the use of benzyltrimethylammonium hydroxide for cleavage can be carried out at lower temperatures and can be concluded after a much shorter reaction time (column 5 lines 22-25). Since the instant claims refer to benzyltrimethylammonium hydroxide and peptide synthesis, Rink is relevant art.

Although Applicants argue that Mihala teach an example that uses a chloroform-phenol solvent system and a different salt and thus teaches away, it is noted that Mihala recite that the art recognizes a wide variety of solvents including DMF, NMP, DMSO, TFE-DCM (page 565 first column). Thus Mihala recognizes the use of more than just chloroform-phenol. Further, Mihala does not discredit the use of any particular solvent system. It is noted that the instant rejection is a multiple reference 103 rejection and as such any single reference does not necessarily anticipate the claims. In the instant case, Rink is the primary reference. Like Rink, Mihala recognizes that the problems with synthesizing long peptides includes decreasing solubility and associations (via van der Waals and hydrogen bonding) between the peptide chains (page 565 first paragraph). Mihala teach that the success of solid phase synthesis is limited by the aggregation of the growing peptide chains (abstract, page 565).Mihala teach that protected amino acids (page 566 section 'general') were used and that coupling steps were carried out with tetrabutyl ammonium salt additive (TBA*ODhbt) (page 566 section 'solid phase synthesis'). Mihala teach that the tetrabutyl ammonium salt additive is used to enhance solubility (page 567 first complete paragraph). Mihala teach that the tetrabutyl ammonium salt additive lead to improved efficiency (title, abstract, Table 1). Mihala suggests that use of the ammonium salt as an additive provides an alternative for improving coupling efficiency in solid phase peptide synthesis (last paragraph page 567). Thus, Mihala provides information on the benefits of using ammonium salt additives. Further, it is noted that the exclusion the applicants refer to only applies is the salt is added in step c) as recited in claim 3. Rink, for example motivates the use of the salt in step a (Rink teach (column 5 lines 7-25, column 8 lines 24-51) that benzyltrimethylammonium hydroxide, for example, can be used to remove the amino protecting

group, for example Fmoc. Rink expressly teach that the use of benzyltrimethylammonium hydroxide for cleavage can be carried out at lower temperatures and can be concluded after a much shorter reaction time (column 5 lines 22-25)).

Although Applicants argue that the effect of the salt in the instant invention is different than in Mihala since the salts of the instant invention improve the elimination of excess of amino acids or cleavage reagents, it is noted that the features upon which applicant relies (i.e., improved elimination of excess amino acids or cleavage reagents) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the prior art suggest the active steps of the claims thus the claim limitations are met. Further, it is noted that MPEP section 2144 IV states that it is not necessary that the prior art suggest the combination to achieve the same advantage.

Although Applicants argue that the references do not teach the use of ammonium salts during the process and Merrifield does not make up for the deficiencies, Rink teach (column 5 lines 7-25, column 8 lines 24-51) that benzyltrimethylammonium hydroxide, for example, can be used to remove the amino protecting group, for example Fmoc which corresponds to step 3a. Thus, Rink suggest the use of benzyltrimethylammonium hydroxide as recited in the claims for a synthesis process. Rink expressly teach that the use of benzyltrimethylammonium hydroxide for cleavage can be carried out at lower temperatures and can be concluded after a much shorter reaction time (column 5 lines 22-25). In summary, Rink Mihala and Merrifield all teach the well-known solid phase peptide synthesis technique. The references teach advantages of including salts specifically ammonium salts at various stages of the process. Rink teach (column 5 lines 7-

25, column 8 lines 24-51) that benzyltrimethylammonium hydroxide can be used to remove the amino protecting group. Rink expressly teach that when benzyltrimethylammonium hydroxide is used that the cleavage can be carried out at lower temperatures and can be concluded after a much shorter reaction time. Merrifield also teach the use of benzyltrimethylammonium hydroxide, specifically during the addition step to enable the chemical reaction (page 1293 section 'acylation'). Further, Mihala addresses the problem of aggregation by using an ammonium salt to increase solubility and decrease aggregation. Since the references show that the art recognizes the use of ammonium salts as additives at various stages of the peptide synthesis process one would have a reasonable expectation of success.

Conclusion

Claims were previously rejected under 103 based on the references cited herein. The rejection is updated based on the claim amendments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ronald T Niebauer/
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654